

Applicant : Ambrose et al.

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Title : USE OF POLYMORPHISMS IN HUMAN OATP-C ASSOCIATED WITH AN EFFECT ON STATIN PHARMACOKINETICS IN HUMANS IN STATIN THERAPY

PROPOSED CLAIMS

1. **(Currently Amended)** A method of diagnosis comprising:
  - (a) providing a biological sample from a human identified as being in need of treatment with rosuvastatin, wherein the sample comprises a nucleic acid encoding OATP-C;
  - (b) testing the nucleic acid for the presence, on at least one allele, of ~~either~~  
~~—— (i) a codon encoding alanine instead of valine at the position corresponding to amino acid position 174 of SEQ ID NO:1; or~~  
~~—— (ii) an allele of a polymorphism in linkage disequilibrium with (i); and~~
    - (c) if ~~either (i) or (ii)~~ the codon encoding alanine is found in at least one allele,diagnosing the human as likely to have reduced ability to transport rosuvastatin into liver cells.
2. **(Withdrawn)** A method according to claim 1 wherein the polymorphism of (b)(ii) is -26A>G, -118A>C, -309T>C, -878A>G, -903C>T, -1054G>T, -1215T>A, or -1558T>C, all of SEQ ID NO:2; or T2122G, C2158T, A2525C, or G2651A, all of SEQ ID NO:3.
3. **(Withdrawn)** A method according to claim 1 wherein the polymorphism of (b)(ii) is selected from -118A>C and -1558T>C of SEQ ID NO:2.
4. **(Currently Amended)** A method according to claim 1, wherein the human is being treated with one dose level of rosuvastatin and step (c) further comprises diagnosing the human as suitable for titration to another higher rosuvastatin dose level if ~~either (i) or (ii) is found in at least one allele~~ encodes alanine instead of valine at amino acid position 174 of SEQ ID NO:1.
- 5-6. **(Canceled)**

7. **(Previously Presented)** A method according to claim 1 wherein the human is being treated with at least 5 mg of rosuvastatin daily.
8. **(Previously Presented)** A method according to claim 1 wherein the human is being treated with at least 10 mg of rosuvastatin daily.
9. **(Previously Presented)** A method according to claim 1 wherein the human is being treated with at least 20 mg of rosuvastatin daily.
10. **(Previously Presented)** A method according to claim 1 wherein the human is being treated with at least 40 mg of rosuvastatin daily.
11. **(Currently Amended)** A method of diagnosis comprising:
- (a) providing a biological sample from a human identified as being in need of treatment with rosuvastatin, wherein the sample comprises an OATP-C polypeptide;
  - (b) determining whether ~~the amino acid of the OATP-C polypeptide corresponding to~~ comprises an alanine instead of a valine at position 174 of SEQ ID NO:1 is a valine; and
  - (c) if the amino acid at position 174 of SEQ ID NO:1 is not a valine an alanine,  
diagnosing the human as likely to have a reduced ability to transport rosuvastatin into liver cells.
12. **(Previously Presented)** A method according to claim 11, wherein the human is being treated with one dose level of rosuvastatin and step (c) further comprises diagnosing the human as suitable for titration to another, higher rosuvastatin dose level if the amino acid is ~~not a valine~~ an alanine.
13. **(Withdrawn)** A method according to claim 11, the method further comprising measuring the level of OATP-C polypeptide expression.

14. **(Withdrawn)** A method according to claim 11, the method further comprising determining, in a sample of nucleic acid from the human, the presence or absence, on at least one allele, of a cytosine at the position corresponding to -118 of SEQ ID NO:2, wherein the presence of the cytosine, combined with the determination that the amino acid of (b) is not a valine, is a further indication that the human is likely to have reduced ability to transport rosuvastatin into liver cells.

15. **(Canceled)**

16-17. **(Canceled)**

18. **(Previously Presented)** A method according to claim 11, wherein the human is being treated with at least 5 mg of rosuvastatin daily.

19. **(Previously Presented)** A method according to claim 11, wherein the human is being treated with at least 10 mg of rosuvastatin daily.

20. **(Previously Presented)** A method according to claim 11, wherein the human is being treated with at least 20 mg of rosuvastatin daily.

21. **(Previously Presented)** A method according to claim 11, wherein the human is being treated with at least 40 mg of rosuvastatin daily.

22. **(Withdrawn)** A method according to claim 1, wherein the nucleic acid is tested both for the presence, on at least one allele, of a codon encoding alanine at the position corresponding to position 174 of SEQ ID NO:1 and for the presence, on at least one allele, of a cytosine at the position corresponding to position -118 of SEQ ID NO:2.